R E M A R K S

The feature of a latanoprost concentration of 0.001 to 0.01% (W/V) added to claim 1 was recited in original claim 2.

New claims 5, 7 and 13 include a feature (latanoprost in a concentration of 0.005% (W/V)) of original claim 4.

New claims 6 and 12 include features of original claims 1 and 2.

New claims 8, 9, 14 and 15 include a feature (ε-aminocaproic acid in a concentration of 0.1 to 2% (W/V)) of original claim 3.

New claims 10, 11, 16 and 17 include a feature (ε-aminocaproic acid in a concentration of 1% (W/V)) of original claim 4.

Submitted concomitantly herewith is a RECORD OF SUBTANCE OF INTERVIEW BY APPLICANTS with respect to the March 17, 2008 telephone interview involving Examiner Webb, Supervisory Examiner Krass and the undersigned.

As discussed in the enclosed RECORD OF SUBSTANCE OF INTERVIEW BY APPLICANTS, during the aforesaid telephone interview, Supervisory Examiner Krass said that to avoid the prior art rejection set forth in the October 19, 2007 Office

Action (rejection of the pending claims over USP 6,011,062 to Schneider et al.), that applicants amend the claims to recitre the time period for the stability and possibly also the degree of the stability.

During the aforesaid telephone interview, the undersigned made an argument that it should not be necessary to amend the claims, since advantages inherent in a claim which render the claim patentable over the prior art need not be recited in the claims. In re Estes, (CCPA 1970) 164 USPQ 519 and In re Merchant, (CCPA 1978), 197 USPQ 785,788 which states as follows:

> "We are aware of no law requiring unexpected results relied upon for patentability be recited in the claims."

As a further reason why it is considered it is not necessary to amend the claims as suggested by the Supervisory Examiner during the aforesaid telephone interview, see the enclosed copy of the title page and page 42 of "Stability of Drugs and Dosage Forms." Said enclosure shows that the accelerated testing described in the present specification corresponds to a long-term room-temperature storage test. The following is an English

translation of the paragraph in the box shown on the enclosed page 142 of the "Stability of Drugs and Dosage Forms":

" Shelf-Life Estimation from Temperature-Accelerated Studies

In temperature-accelerated studies, shelf life at a storage temperature T_1, is estimated from the shelf life at an elevated temperature T_2, according to

$$\ln \frac{t_{90(T1)}}{t_{90(T2)}} = \frac{Ea}{R}\left(\frac{1}{T1} - \frac{1}{T2}\right) \qquad (115)$$

Shelf life is referred to as $t_{90(T2)}$ when the lower specification limit of content is 90%. The shelf life exhibits a long-linear relationship versus 1/T in a given temperature range when the activation energy is constant (Fig. 266). The latter condition usually is met only when the degradation mechanism is the same across the temperature range of exposure. For example, a shelf life of 6 months at 40 corresponds to a shelf life of 3 years at 25°C when an activation energy of 22.1 kcal/mol is assured."

Applicants have informed the undersigned that in the field of ophthalmic solutions, long-term preservation stability at room temperature is generally estimated by conducting an accelerated testing. Applicants have also informed the undersigned that according to the enclosed "Stability of Drugs and Dosages Forms",

for example, the shelf life of "6 months at 40°C" correspond to that of "3 years at 25°C" (see Fig. 266 of the enclosure).

As is apparent from data of the accelerated testing described in the present specification (see the test results for 50°C to 80°C in Table 3 on page 16 of the specification), ① adjustment of the pH of the solution to 5.0 to 6.25 or ② addition of ε-aminocaproic acid to the solution enables the ophthalmic solution to be stored for a long period of time at room temperature.

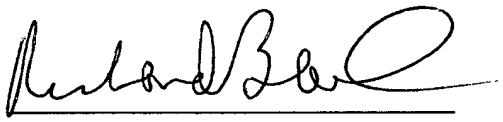
Table 3 of the present specification shows that after storage at 50°C for 8 weeks, the residual ratio of the latanoprost in an ophthalmic solution is 93.1% when ε-aminocaproic acid is added to the solution. Moreover, Table 3 shows that after storage at 80°C for 4 weeks, the residual ratio of latanoprost is 51.8% when ε-aminocaproic acid is added, whereas the residual ratio of latanoprost is 6.3 to 28.9% when ε-aminocaproic acid is not added. Thus, applicants' Table 3 clearly shows that the stability of latanoprost in an ophthalmic

solution is significantly improved when ε-aminocaproic acid, out of numerous existing additives, is added.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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RSB/ddf

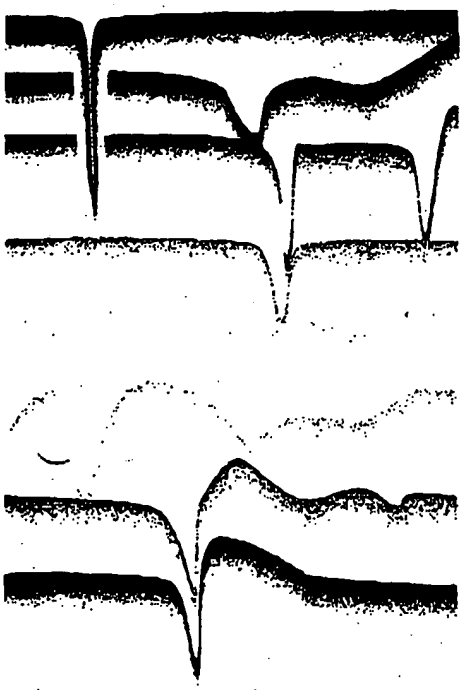
Enc.: copy of the title page and page 42 of
"Stability of Drugs and Dosage Forms"

Stability of Drugs and Dosage Forms

医薬品の安定性

―よりよい開発と評価のための基礎から実際まで―

国立衛生試験所　吉岡澄江　著



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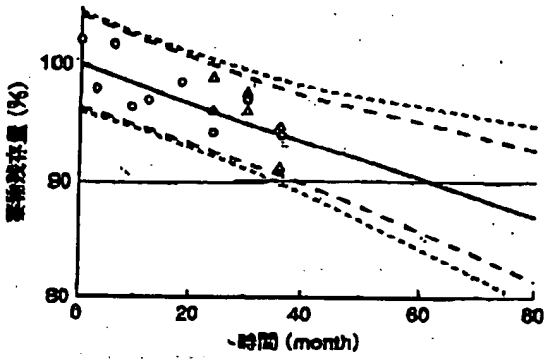

図 265 薬物の残存率-時間曲線の 95% 信頼限界[749]
2%/ year のゼロ次分解，SD 2% の定量誤差を仮定．
----：データ（○）から求めた 95% 信頼限界．
－－：データ（△）を加えて求めた 95% 信頼限界．

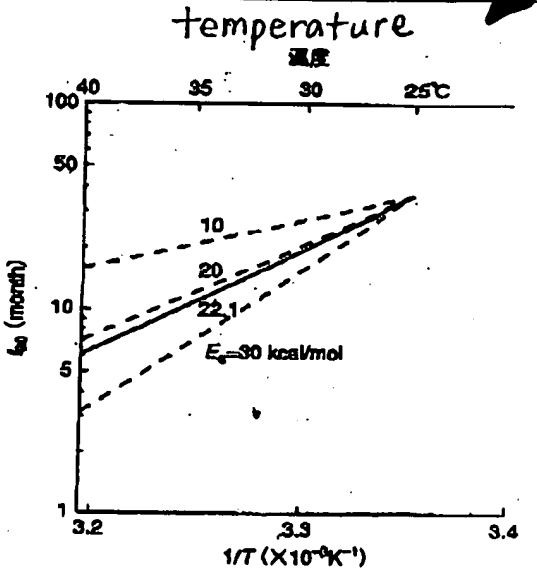

図 266 有効期間の温度依存性

Fig. 266
Temperature dependence of shelf life

Woolfe の式が C から t を推定するときに用いられるのに対して，t から C を推定する場合には Carstensen の式（114 式）が用いられる[750]．

$$C_t=\bar{C}+b(t-\bar{t})\pm t'\left[1+\frac{1}{n}+\frac{(t-\bar{t})^2}{S_t}\right]V_e \qquad (114)$$

114 式を用いれば，ある時間における C の値を推定することができる．

2 加速試験データに基づき温度に対する外挿によって推定する方法

加速温度条件 T_2 において求められた有効期間 $t_{90(T_2)}$（規格下限値が 90% の場合）に基づいて実際の保存温度 T_1 における有効期間 $t_{90(T_1)}$ を推定する場合には 115 式を用いる．ここで有効期間を支配する化学的変化の機構が同一である温度領域では，図 266 のように直線関係で表すことができる．直線の勾配は活性化エネルギーによって決まる．T_2：40℃での 6 か月が T_1：25℃での 3 年に相当するのは，E_a が 22.1 kcal/mol の場合である．

$$\ln\frac{t_{90(T_1)}}{t_{90(T_2)}}=\frac{E_a}{R}\left(\frac{1}{T_1}-\frac{1}{T_2}\right) \qquad (115)$$

2-1 加速試験の実験計画

有効期間と温度との関係を明らかにするための加速試験を合理的に行う実験計画としては，すでに 1960 年代に Tootill[751]，Kennon[752]，Lordi[753] らによって提案されている．

Lordi は 41.5℃および 60℃での加速試験データから，有効期間を推定するための実用的なチャート（図 267）を報告している．コンピュータが普及した現在ではほとんど利用価値がない